# Prediction of Surgical Resectability in Patients with Hepatic Colorectal Metastases

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## **Objective**

To evaluate the efficacy of two distinct imaging techniques to predict, before operation, unresectability compared with standard computed tomographic scan (CT).

## **Summary Background**

Accurate preoperative identification of the number, size, and location of hepatic lesions is crucial in planning hepatic resection for colorectal hepatic metastases. Although infusion-enhanced CT is the standard, its limitations are the imaging of relatively isodense and/or small (<1 cm) lesions. The increased sensitivity of CT arterial portography (CTAP) may be offset by false-positive results caused by benign lesions and flow artifacts.

## **Methods**

Fifty-eight selected patients considered to be eligible for resection by standard CT had laparotomy. Before operation and in addition to CT, all patients had CT arterial portography and hepatic artery perfusion scintigraphy (HAPS) using radiolabeled macroaggregated albumin. Early studies showed an increased sensitivity for detecting small lesions using the invasive CTAP. Similarly, the HAPS study has detected malignant lesions not observed by standard CT.

# Results

Of 58 patients having laparotomy, 40 were resectable by either lobectomy (22) or trisegmentectomy (1) and the rest by single or multiple wedge resections. Eighteen patients could not be resected because of combined intra- and extrahepatic disease or the number and location of metastases. Standard CT detected 64% of all lesions (12% of lesions less than 1 cm). Unresectability was accurately predicted by CTAP and HAPS in 16 (88%) and 15 (83%), respectively, of the 18 patients considered ineligible for resection at laparotomy. Of the 40 patients who had resection for possible cure, CTAP and HAPS falsely predicted unresectability in 6 of 40 patients (15%) and in 10 of 40 patients (25%), respectively. The positive predictive value for unresectability of CTAP and HAPS was 73% and 60%, respectively. False-positive lesions after CTAP included hemangiomas, cysts, granulomas, and flow artifacts. False-positive HAPS lesions included patients in whom no tumor was found at surgery but with some identified by intraoperative ultrasound, blind biopsy, and blind resection.

## Conclusions

False-positive results by HAPS and CTAP may limit the ability of these tests to accurately predict unresectability before operation and may deny patients the chance for surgical resection. The

HAPS study does, however, detect small lesions not seen by CT or CTAP. Standard CT, although less sensitive, followed by surgery and intraoperative ultrasound, does not necessarily preclude patients who could be resected.

The surgical approach to patients with hepatic colorectal metastases ranges from aggressive resection of multiple lesions to a more philosophic approach that considers overall survival statistics and perioperative rates of morbidity and mortality. <sup>1-4</sup> However, consistent with present statistics documenting a 25% to 30% 5-year survival rate, patients with colorectal hepatic metastases are considered candidates for resection. <sup>5</sup>

Accurate preoperative identification of the number, size, and location of hepatic metastases is essential in planning surgical procedures. The ability to predict unresectability before operation remains controversial. Intravenous infusion-enhanced computed tomographic scan (CT) has been the standard for preoperative detection of hepatic metastases. Its limitations, however, are the imaging of relatively isodense and/or small (less than 1 to 2 cm) lesions, visualization of extrahepatic disease, and the inability to distinguish between benign from malignant tumors. 6.7 The decreased sensitivity of CT to detect metastatic lesions has not been improved with magnetic resonance imaging, although the latter accurately diagnoses lesions such as hemangiomas and cysts. 8 Many recent reviews have documented the efficacy of CT angiography (superior mesenteric arterial portography) in detecting small hepatic lesions not seen by standard CT.6.7,9-13 The increased sensitivity (80% to 90%) of CT arterial portography (CTAP) has been associated with increased false-positive diagnoses because of flow artifacts, cysts, small benign tumors, and in some cases no lesions detected.14-16

A natural selection process exists because most patients referred for surgery and possible resection have been prescreened using the noninvasive techniques of CT and magnetic resonance imaging. Patients are often considered ineligible for surgery when the standard CT examination shows extensive, bilobar, or extrahepatic disease, which precludes resection for possible cure.

An ideal imaging technique would detect small metastatic lesions and distinguish tumor from flow artifacts, blood vessels, or cystic lesions and might avoid unnecessary surgery. Recent advances in nuclear medicine techniques combined with the availability of triple-headed single photon emission CT systems for imaging have

It has been our experience that a fair amount of ambiguity exists when prospectively reviewing these imaging techniques with the radiologists before surgery. Because most authors agree that standard CT detects only 40% to 80% of lesions in general (10% to 15% smaller than 1 cm), the overall efficacy and cost-effectiveness of these newer preoperative invasive techniques must be considered. Most surgeons want to avoid unnecessary surgery in patients who cannot be cured, but few want to refuse patients the chance for surgery based on false-positive predictions of multiple lesions or unresectability. We must still determine which subgroups of patients might benefit from preoperative detection or heightened awareness of multiple lesions detected by invasive techniques and whether surgeons should rely on noninvasive techniques followed by laparoscopy and possibly open surgery. We began this study, therefore, to evaluate the efficacy of two separate and distinct types of invasive diagnostic imaging techniques (CTAP and HAPS) to predict unresectability in patients considered potentially eligible for resection by standard intravenous infusion-enhanced CT.

### **METHODS**

During a 2-year period, 58 highly selected patients with suspected or biopsy-proved hepatic colorectal metastases were considered for this study. All patients had repeated plain and intravenous infusion-enhanced CT examination from 2 days to 3 weeks before surgery. Within 48 hours of surgery, all patients had arteriography, CTAP, and HAPS. There were 42 men and 16 women, with a mean age of 52 years (range, 31 to 78 years). Some patients also had intraoperative ultrasound examination.

Plain and intravenous infusion-enhanced CT scans were performed using a General Electric (GE) 9800 body scanner (General Electric Medical Systems, Milwaukee, WI). During this study, however, there were several upgrades through the GE 9800 Quick up to the GE 9800 Advantage High Speed Scanner. Basic arteriography was performed with celiac axis and superior mesenteric artery injections, with evaluation by digital subtraction techniques. Computed tomographic arterial portogra-

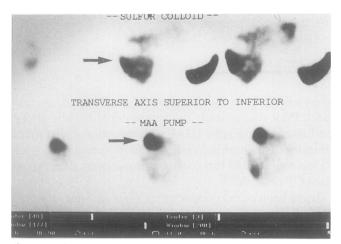
shown promise in the detection of small hepatic metastases. Pilot studies using the technique of hepatic artery perfusion scintigraphy (HAPS) using radiolabeled macroaggregated albumin has shown an increased sensitivity for detecting small tumor lesions not seen by either standard CT or CTAP.<sup>17</sup>

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**Figure 1.** Standard sulfur colloid nuclear medicine scan demonstrates a space occupying metastatic lesion (arrow above). Hepatic artery infusion scintigraphy (MAA) demonstrates positive uptake of macroaggregated albumin into this metastatic lesion (arrow below).

phy was performed through injection through the superior mesenteric artery. In the rare case of superior mesenteric artery obstruction, the splenic artery was used. When the right hepatic artery branched off the superior mesenteric artery, catheter injection was performed distal to the takeoff of the replaced right hepatic artery. After catheterization, the patient was placed on the CT scanner. Conray 30 (Mallinckrodt Medical Inc., St. Louis, MO) was injected at a rate of 3 mL per second for a total of approximately 300 mL. In most cases, a standard 15-second delay allowed adequate portal venous phase imaging.

The technique of hepatic artery infusion scintigraphy has been described.<sup>17</sup> After CTAP, catheters were replaced to the common hepatic artery just distal to the origin of the gastroduodenal artery. Sometimes two injections into an aberrant right hepatic or left hepatic artery were necessary. After the slow infusion of technetium-99m-macroaggregated albumin, the patients were imaged in the Nuclear Medicine department using a high-resolution single photon emission CT imaging technique with a three-headed camera. Images can be reconstructed in transverse, coronal, and sagittal planes. Compared with standard liver spleen scan, positive results are seen as hot spots," with the intensity of imaging correlating with the volume of tumor uptake of the macroaggregated albumin molecule (Fig. 1). Not infrequently inadvertent infusion into the gastroduodenal artery shows uptake into the duodenum, gallbladder, or both after nuclear imaging. These are usually well delineated.

Resectability was the surgeon's objective and subjective decision and was determined by factors including number, size, and location of colorectal metastases. In general, patients with more than four bilobar metastases had cryosurgery or alcohol ablation instead of formal re-

section, although in several cases bilobar multiple wedge resections were performed.

Results showing whether CTAP or HAPS could predict unresectability before operation are expressed on a per-patient basis. Patients who could be resected at surgery but had many preoperative lesions that suggested unresectability were considered to have false-positive results if these extra lesions proved not to be tumor or could not be found at surgery. Sensitivity for unresectable predictions was calculated as true-positive results divided by the true-positive plus false-negative results. The positive predictive value for unresectability was the truepositive result divided by true-positive plus false-positive results. Of equal importance, however, was the predictive value for both unresectable (U) and resectable (R) predictions. This was calculated as the number of accurate predictions (U + R) divided by the number of tests performed.

#### **RESULTS**

Fifty-eight patients were considered potentially resectable based on the results of standard CT and had exploratory laparotomy. A total of 145 lesions were detected at surgery. Standard CT detected 64% of all lesions found at surgery and 12% of lesions estimated to be less than 1 cm in diameter. Computed tomographic arterial portography and HAPS detected 86% and 92%, respectively, of lesions identified at surgery. Hepatic artery perfusion scintigraphy did not detect cysts, some benign tumors (hemangiomas), and lesions found at surgery that were masked by isotope uptake into the duodenum or gallbladder on nuclear imaging. Forty-eight per cent of patients had a single lesion, whereas the other patients had two or more lesions. Forty of 58 patients (68%) were considered resectable and had hepatic resection. There were 22 lobectomies, 1 trisegmentectomy, and the remaining patients had wedge resection, multiple wedge resections, or left lateral lobectomy with wedge resections. Eighteen patients were considered unresectable because of combined intra- extrahepatic disease in 3 and the number, size, or location of metastases in 15. Vascular involvement or proximity to major vessels were included in the 15 unresectable patients. Table 1 shows overall resectability and unresectability, including predictions for both invasive imaging techniques. These invasive techniques accurately predicted unresectability in 16 of 18 (88%) and 15 of 18 (83%) patients, respectively. Unfortunately, of the 40 patients who had resection for potential cure, CTAP falsely predicted unresectability in 6 of them (15%). Lesions observed by preoperative CTAP that falsely predicted unresectability included hemangiomas, cysts, granulomas, and many flow artifacts. In 2 patients, lesions could not be detected even with intraoperative ultrasound. Of the 40 patients who had hepatic

Table 1.			
	Surgery		
	Unresectable	Resectable	Total (Actual)
HAPS			
Unresectable (U)	15	3	18 U
Resectable (R)	10	30	40 R
Total	25	33	58
CTAP			
Unresectable (U)	16	2	18 U
Resectable (R)	6	34	40 R
Total	22	36	58

HAPS = hepatic artery perfusion seintigraphy; CTAP = computed tomography during arterial portography.

resection, HAPS predicted unresectability in 10 of 40 resectable patients (false-positive rate, 25%). At surgery, however, intraoperative ultrasound accurately identified 3 more metastatic lesions in 2 patients, and these were removed by wedge resection in addition to the primary resection in the other lobe. Another patient had a blind resection" of the left lateral segment revealing tumor on cut sections. A fourth patient had a wedge resection after 4 blind" needle biopsies, with the last yielding tumor on frozen section. In 6 patients, the HAPS study predicted extensive bilobar disease. In addition to the primarily resectable lesion, tumor could not be found in the opposite lobe in these patients. There were also several benign lesions identified that could explain the false-positive HAPS result. In 2 of the 6 patients, follow-up CT at 4 and 6 months revealed what appeared to be metastatic lesions in the areas that previously showed uptake in the HAPS study. These lesions were not confirmed pathologically but we were suspicious that the HAPS study detected tumor in the opposite lobe that was either too small to be visualized or palpated during surgery. On a per-patient basis, the false-positive rate was not changed because all 10 patients were resectable. Intraoperative ultrasound would certainly have decreased the false-positive rate on a per-lesion calculation. In 5 patients lesions were detected by the HAPS study and documented at surgery but were not predicted by CTAP. Most of these small metastatic lesions, although defining the efficacy of the HAPS study, did not alter the predicted resectability/ unresectability rate. Computed tomographic arterial portography detected no lesions in the left lateral segment of the patients who had blind resection and blind biopsy. And CTAP did not detect lesions in the HAPS patients who were identified as having probable metastatic deposits 4 and 6 months after surgery.

The sensitivities for predicting unresectability of CTAP and HAPS (88% and 83%) were statistically similar. The important positive predictive value of unresect-



**Figure 2.** Computed tomographic arterial portography in a patient with a previously demonstrated large right lobe lesion. This cut suggests numerous lesions in the right lobe lesion with a possible cyst in the left lateral segment (arrow).

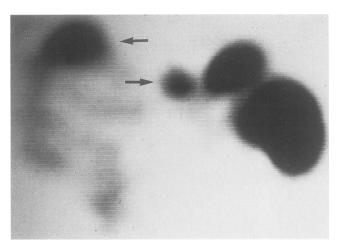
ability, which takes into account false-positive predictions, was 73% for CTAP and 60% for HAPS. The predictive value for accurately predicting both resectable and unresectable patients was 77% and 86% after HAPS and CTAP, respectively.

### **DISCUSSION**

We tried to evaluate the ability of two separate invasive imaging techniques to determine operability and resectability prospectively. A natural bias exists, however, because all patients were considered potentially resectable by standard intravenous infusion-enhanced CT. A second bias is that most patients were adequately prescreened before referral, and those deemed ineligible for surgery usually received chemotherapy. We know this to be true because many of our referrals have been declared chemotherapy failures" despite having potentially resectable metastatic lesions.

In this study, the surgeons consulted with three groups of radiologists before preoperative prediction of unresectability (CT body imaging, invasive radiologists, and nuclear medicine). Although most studies have compared the sensitivity and positive predictive value of one test with those of other tests, we found that the imaging techniques often complimented one another in determining whether a lesion existed. Figure 2 demonstrates a case of a patient with an obvious large dome lesion on CT. Computed tomographic arterial portography demonstrated this lesion but, in other cuts, showed numerous possible defects in the central right lobe and left lateral segment. The radiologists were unsure whether these were flow artifacts or cysts. The HAPS study (Fig. 3) accurately and definitively visualized a large amount of uptake in the dome and an obvious discrete lesion in the

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**Figure 3.** Hepatic artery perfusion scintigraphy in the patient from Figure 2 accurately demonstrates uptake in the large dome lesion on the right (arrow) and an obvious discrete lesion in the left lateral segment (arrow) near the splenic and gastric uptake of the macroaggregated albumin. The left lateral segment lesion was seen as a cyst in Figure 2.

left lateral segment (near the spleen and stomach). The HAPS study allowed the invasive radiologist to feel more secure in the diagnosis of one more separate and distinct tumor nodule. Although this represents a bias and is considered unblinded," it also represents the reality of preoperative imaging techniques. In Figure 4, CT shows an obvious right lobe lesion. Computed tomographic arterial portography showed many dome lesions, which can be seen retrospectively on secondary review of the CT. The HAPS study (Fig. 5) unequivocally reveals multiple lesions throughout the liver, with a large massive tumor in the right lobe surrounded by at least four separate nodules. Several nodules can be seen near the uptake in the gallbladder, with many nodules in the left lobe. The HAPS study in this case predicted unresectability, although the CTAP detected one possible lesion and a flow artifact in the left lateral segment. At surgery, many small tumor lesions were easily identified in the left medial and left lateral segments.

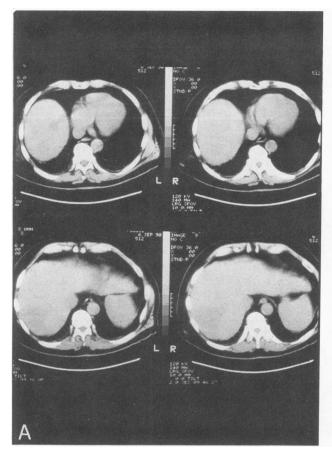
In this study, CTAP and HAPS had a positive predictive value for unresectability of 73% and 60%, respectively. These results are similar to those reported by Sitzmann and colleagues, who reported positive predictive values in predicting a surgical procedure of 77%, 70%, and 55% for arteriographically enhanced CT, magnetic resonance imaging, and CT, respectively. In this study, the number of false-positive predictions for unresectability indicates that those patients would be denied potentially curative surgery. The HAPS study represented an interesting phenomenon. Intraoperative ultrasound, blind resection, and blind biopsies allowed us to resect tumor that was not easily identified at surgery. Preoperative uptake by HAPS in these areas suggested extensive bilobar disease and unresectability. Early in our study,

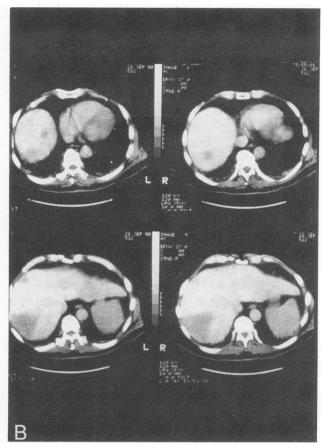
these findings would have precluded resection. During the course of this study we took a more aggressive approach to multiple wedge resections for possible cure.

Most radiologic reviews have documented a high sensitivity rate of CTAP to detect small lesions. Although several studies found very low false-positive rates, 18 recent reviews have contradicted this initial enthusiasm. 15,16 In a series of 52 patients who had CTAP, 8 patients had a total of 10 false-positive findings, yielding a false-positive rate of 15%. 14 The reason for false-positive diagnoses in this series included cirrhosis, fatty infiltration, portal perfusion defects, and unknown causes. Although newer techniques such as continuous CT angiography have increased the sensitivity rate to 98%, 18,19 other investigators continue to document a fairly high false-positive diagnosis rate after CTAP. The fact that technical failures have been implicated in this false-positive rate does not alter the decreasing efficacy of this method to accurately predict unresectability before operation.15

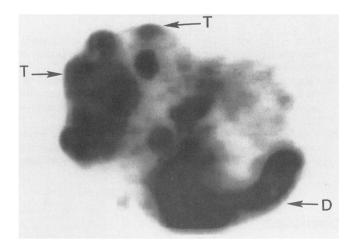
The use of HAPS in this study did not improve either the positive predictive value for predicting unresectability (60%) or the sensitivity (83%) compared with CTAP. Although CTAP accurately detects most lesions found at surgery, the HAPS study predicts tumor that is not found at surgery, that is only found at blind resection or blind biopsy, and may even not be detected until months after operation. The decreased positive predictive value and predictive value of the HAPS study on a per-patient basis is due to the number of false-positive predictions of unresectability (25%) and the decreased ability to resect lesions that cannot be palpated or visualized by intraoperative ultrasound.

The nature of the terms operability" and resectability" may be rapidly changing. Early reports documented decreased survival in patients with multiple liver metastases who had resection compared with patients with solitary lesions. 20-22 Others, however, have suggested that there is no statistical difference in survival rates in patients with single compared with multiple hepatic metastases.<sup>23,24</sup> Some series have suggested that performing multiple wedge resections with adequate margins does not statistically decrease survival time. 25,26 Minton and associates have described multiple resections of as many as 13 hepatic metastases with favorable early survival. The question, of course, is whether resections such as these are potentially curable or whether survival time is delayed.<sup>27</sup> In our study, the HAPS technique definitely detected what appears to be tumor metastases that were not identified at surgery. The HAPS technique also suggested extra tumor lesions in patients considered unresectable during surgery. Although the HAPS study accurately predicted unresectability on a per-patient basis in this group, there was more suspected tumor seen radiologically than could be accounted for at surgery. It is un-





**Figure 4.** (A) Standard infusion enhanced CT demonstrating a large (but diffuse) right posterior lesion. There is a suggestion of dome lesions on the right. (B) Computed tomographic arterial portography accurately delineates numerous lesions in the right posterior, right dome, and left medial segments of the liver. There also is a suggestion of metastatic lesions in the left lateral segment.



**Figure 5.** Hepatic artery perfusion scintigraphy easily demonstrates the large right posterior lesion from Figure 4, numerous lesions in the dome of the liver and scattered metastatic deposits throughout the liver including left medial and left lateral segments. At least 15 lesions were confirmed at surgery. T = tumor, D = uptake into the duodenum.

clear whether these studies can predict recurrences in patients who have resection. Further CT follow-up in these patients and correlation of recurrences with the preoperative HAPS study are needed to answer this question.

Although highly accurate predictions of lesions and unresectability can be made before surgery using invasive techniques, the question remains as to whether patients can be denied a chance for operation and potential cure because of false-positive diagnoses. If CTAP were used before operation to make the decision, then 16 of the 18 unresectable patients would have avoided unnecessary surgery. Conversely, however, 6 of the 40 resectable patients would have been denied potentially curable surgery because of false-positive predictions of unresectability. If the HAPS study were used before operation, 15 of 40 resectable patients would have avoided an unnecessary operation. On the other hand, because of falsepositive predictions of unresectability, 10 of the 40 resectable patients would have been denied a potentially successful operation. Most surgeons would prefer to be more inclusive rather than exclusive in acting on preoperative predictions. This study did not allow us to make 514 Vogel and Others Ann. Surg. • May 1994

accurate enough predictions to be used before surgery. It did, however, show the ability of invasive imaging techniques to detect small metastatic lesions not seen on standard intravenous infusion-enhanced CT.

The choices confronting the surgeon are varied and difficult. If there is a role for preoperative identification of the number and location of suspected metastases. even in patients who appear potentially resectable, then an obvious choice might be invasive techniques followed by laparoscopy in a further attempt to predict resectability before open surgery. Recent reports showed that the newer spiral CT after arterial portography detected metastatic lesions as small as 5 mm and showed sensitivities equal to intraoperative ultrasound.<sup>28,29</sup> If these results can be substantiated in other studies, then invasive techniques will certainly play an important role in preoperative decision making. If cost-effectiveness, patient inconvenience, and hospital days are important issues, another option might be CT followed by laparoscopy to determine resectability and the decision for open surgery. Further studies, newer technology, and changing survival statistics may enable the surgeon to make better preoperative decisions.

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#### **Discussion**

DR. JAMES V. SITZMANN (Baltimore, Maryland): The paper is a well-prepared study designed to answer a very straightforward and essential question for the cancer surgeon: is the hepatic tumor resectable? This question also implies a couple other questions. Does the tumor need to be resected? Is it be-